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Circulating levels of novel adipocytokines in patients with colorectal cancer

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ABSTRACT

Objective: Adipocytokines have been reported to contribute to the pathogenesis of colorectal cancer (CRC). The aim of this matched case-control study was to explore circulating novel adipocytokines, such as serum visfatin, omentin-1 and vaspin levels in patients with CRC.
Method: Serum visfatin, omentin-1, and vaspin levels were measured in 69 subjects (39 patients with colorectal cancer and 30 age- and sex-matched healthy controls) using enzyme-linked immunosorbent assay (ELISA) methods.
Results: Compared with the controls, patients with CRC had significantly higher circulating omentin-1 (203.23 vs 9.12 ng/ml, $p < 0.0001$) visfatin (4.03 vs 2.01 ng/ml, $p < 0.0001$) and vaspin (0.54 vs 0.31 ng/ml, $p = 0.015$) levels. After adjustment for covariates (age and body mass index), patients with CRC had significantly higher serum omentin-1 ($p < 0.0001$), visfatin ($p < 0.0001$), and vaspin ($p = 0.040$) levels than the control group. Furthermore, the results did not change when age and waist-to-hip ratio were considered as covariates in the general linear models.
Conclusions: The observed higher levels of omentin-1, visfatin, and vaspin in patients with CRC, independent of measures of obesity, suggest that these adipocytokines may have a potential role in the development of CRC through mechanisms other than the indirect mechanisms that are active in the association between obesity and CRC.

1. Introduction

The link between obesity and many human malignancies, including colorectal cancer (CRC), has been clearly illustrated in many epidemiological studies [1,2]. Overall, obese individuals are approximately 1.5–2 times more at risk of developing gastrointestinal cancers than normal weight individuals [1].

According to the International Agency for Cancer Research (IACR), there is sufficient evidence in humans for a causal link between overweight and obesity and cancer of the colon [3]. However, the mechanistic basis of these relationships remains incompletely understood.

Although the pathophysiological mechanisms underlying obesity in relation to CRC are likely complex, increased insulin and insulin-like growth factor signaling, intestinal microbiome, chronic inflammation, and adipocytokines have already been postulated as contributors.

Adipocytokines are protein factors that show a number of important systemic complex interactions and influence a large number of different organ systems [4]. They have recently become the focus of research on the role of obesity in carcinogenesis. Several adipocytokines, namely leptin, adiponectin, visfatin and resistin, have been under investigation in a multitude of robust in vitro and epidemiological studies carried out to clarify the association between obesity and CRC [5–12].

A decreased level of adiponectin was recognized as a strong risk factor for early CRC [6]. Two types of adiponectin receptors,

Abbreviations: CRC, colorectal cancer; IACR, International Agency for Cancer Research; AMPK, adenosin monophosphate-activated protein kinase; mTOR, mammalian target of the rapamycin; Nampt, nicotinamide phosphoribosyltransferase; PBEF1, pre-B cell-colony enhancing factor; BMI, body mass index; ELISA, enzyme-linked immunosorbent assay; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WHR, waist to hip ratio; CV, coefficient of variance; GLM, general linear model; NAD, nicotinamide adenine dinucleotide; PARP, poly (ADP-ribose) polymerase; TNF, tumor necrosis factor; eNOS, endothelial nitric oxide synthase; PI3K, phosphoinositide 3-kinase; OLETF, Otsuka Long-Evans Tokushima fatty; TNM, tumor-node-metastasis; FBS, fasting blood sugar; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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AdipoR1 and AdipoR2, may be intimately related to the progression of CRC [13]. Adiponectin can repress colon cancer cell proliferation through AdipoR1- and –R2-mediated adenosin monophosphate-activated protein kinase (AMPK) activation [14]. Under decreased circulating adiponectin levels, AMPK activity is suppressed, and the mammalian target of the rapamycin (mTOR) and the members downstream in the pathway are activated. These changes directly promote colonic epithelial cell proliferation and induce colorectal carcinogenesis [15].

The results of a large case-control study suggested that adiponectin might decrease the risk of colorectal neoplasia by interfering with leptin; conversely, leptin could exert a carcinogenic effect under the condition of a lower abundance of adiponectin [5]. Therefore, the concurrent assessment of adiponectin and leptin may be a helpful prognostic marker in the management of patients with CRC [16].

Visfatin, which is identical to the "pre-B cell-colony enhancing factor (PBEF1)" and "nicotinamide phosphoribosyltransferase (Nampt)," is secreted abundantly by the visceral fat of humans and mice and mimics the action of insulin [17]. There is accumulating evidence to support an interesting connection between PBEF1/Nampt/Visfatin and cancer [18,19]. PBEF1/Nampt/Visfatin may have pro-angiogenic activity, which is highly expressed in some types of tumors, including malignant astrocytomas/glioblastomas, ovarian cancers, gastric and CRC [20–23]. The results of a case-control study suggested that visfatin and resistin might be good biomarkers of colorectal malignant potential and stage progression, independent of the body mass index (BMI) [9].

Omentin-1 is a novel 34 kDa adipocytokine that is selectively and highly expressed in visceral adipose tissue compared with subcutaneous adipose tissue [4,24]. Vaspin (visceral adipose tissue-derived serpin), a member of the serine protease inhibitor family, is also a novel adipocytokine with insulin-sensitizing effects [25].

Against the background of previous research on the contribution of adipocytokines to the pathogenesis of CRC, investigating the circulating levels of novel adipocytokines, such as omentin-1, visfatin and vaspin may be useful to illustrate some pathophysiological aspects of adipose tissue involvement in the development of CRC. The present matched case-control study sought to explore for the first time the concentrations of serum omentin-1 and vaspin and assess visfatin levels in patients with CRC.

2. Methods

2.1. Patients and controls

Thirty-nine consecutive new patients (mean age ± SD 56.72 ± 9.25 years: 23 women and 16 men) who had undergone colonoscopy at Imam Khomeini University Hospital and had been histopathologically diagnosed with CRC by hospital pathologists were enrolled in the study in June 2008. All patients in the sample met the following criteria: no curative medication for CRC; no previous history of malignancy or colorectal operations; no diagnosis of any inflammatory bowel disease, including ulcerative colitis and Crohn's disease; no diagnosis of familial adenomatous polyposis or acromegaly.

We selected a healthy age- and sex-matched control group (mean age ± SD 53.03 ± 6.14 years: 15 women and 15 men) from participants in the Persian Gulf Healthy Heart Study. The Persian Gulf Healthy Heart Study, a prospective population based cohort study, was designed to determine the risk factors for cardiovascular diseases among the northern Persian Gulf population. Detailed information about the methods and procedures of this study is available elsewhere [26].

The participants in the control group had anthropometric measurements comparable with those of the CRC group (Table 1).

Venous blood was obtained from all patients and healthy controls in a fasting state. All the sera were kept frozen at −70 °C until they were used. The study was approved by the medical–ethical committee of Bushehr University of Medical Sciences, and written informed consent was obtained from all subjects.

2.2. Measurements

2.2.1. Physical measurements

Blood pressure was assessed twice at the right arm after a 15-min rest in the sitting position, using a standard mercury sphygmomanometer.

A stadiometer was used to measure height and weight. Heavy outer garments and shoes were removed before the participants' height and weight were measured. Body mass index (BMI) was calculated. Waist circumference was defined at the midway level between the costal margins and the iliac crests. Hip circumference was measured at the level of the greater trochanters. Waist-to-hip ratio (WHR) was calculated for all participants.

2.2.2. Biochemical measurements

A fasting blood sample was taken, all samples were promptly centrifuged, and sera were separated and kept frozen at −70 °C until they were used. On the day of blood collection, analyses for biochemical parameters (blood glucose, triglyceride, and cholesterol levels) were carried out at the Persian Gulf Health Research Center with a Selectra 2 autoanalyzer (Vital Scientific, Spankeren, the Netherlands). Glucose was assayed by the enzymatic (glucose oxidase) colorimetric method using a commercial kit (Pars Azmun Inc., Tehran, Iran). Serum total cholesterol and HDL (high-density lipoprotein) cholesterol were measured using cholesterol oxidase phenol aminoantipyrine. Triglycerides were measured using the glycerol-3 phosphate oxidase phenol aminoantipyrine enzymatic method. Serum LDL (low-density lipoprotein) cholesterol was calculated using the Friedwald formula. LDL cholesterol was not calculated when the triglycerides concentration was >400 mg/dl.

To detect visfatin and vaspin in the serum samples, commercially available (Cat. No. V0523EK and Cat. No. V0712EK, respectively) enzyme-linked immunosorbent assay kits (AdipoGen, Seoul, Korea) were used according to the manufacturer's instructions. The assay sensitivity for visfatin was 0.10 ng/ml; the intra- and interassay coefficients of variance were 3.8–5.5% and 6.4–9.5%, respectively. The assay sensitivity for vaspin was 0.012 ng/ml; the intra- and inter-assay coefficients of variance were 1.3–3.8% and 3.3–9.1%, respectively.

Serum omentin-1 concentrations were measured by manual omentin-1 (human) detection (ELISA kit (intelectin-1 (human) ELISA kit, Apotech Corporation, Switzerland)). The detection limit of the assay was 0.4 ng/ml (range 0.5–32 ng/ml). The mean intraassay and interassay CVs of the omentin-1 assay were 4.51–7.4% and 4.19–9.27%, respectively. The antibodies used in this kit are specific to the measurement of natural and recombinant human omentin-1.

2.3. Definitions

The cutoff points of serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) distributions used to assign subjects to different levels of risk were those derived from the National Cholesterol Education Program (NCEP) guidelines in the United States (Adult Treatment Panel [ATP] III) [27].

The tumor-node-metastasis (TNM) staging for colorectal cancer defined by the American Joint Committee on Cancer (AJCC), 7th

Table 1
The general characteristics, including blood pressure and anthropometric measurements, and the biochemical parameters of patients with colorectal cancer (CRC) and healthy controls.

Variables	Colorectal group (n = 39)	Control group (n = 30)	p Value
Female/male ratio	23/16	15/15	0.458
Age (years)	56.72 ± 9.25	53.03 ± 6.14	0.064
SBP (mmHg)	118.82 ± 17.29	120.21 ± 14.85	0.732
DBP (mmHg)	75.66 ± 11.63	78.14 ± 9.40	0.357
WH ratio	0.94 ± 0.07	0.91 ± 0.08	0.163
BMI (kg/m^2)	26.07 ± 4.58	27.15 ± 3.69	0.300
FBS (mg/dl)	137.48 ± 57.20	76.89 ± 20.37	<0.0001
Total cholesterols (mg/dl)	221.61 ± 51.87	221.53 ± 43.89	0.407
Triglycerides (mg/dl)	131.00 ± 52.97	190.50 ± 117.38	0.007
HDL-C (mg/dl)	42.43 ± 14.48	42.83 ± 9.25	0.900
LDL-C (mg/dl)	153.12 ± 42.40	131.82 ± 30.00	0.026

DBP = diastolic blood pressure, FBS = fasting blood sugar, SBP = systolic blood pressure

edition, revised in 2010 was used to evaluate the cancer staging [28].

2.4. Statistical analysis

Normal distribution of the data was controlled with the Kolmogorov–Smirnov test. Probability values <5% were considered statistically significant. The significance of the difference in the results between the two groups was determined with chi-square analysis using 2 × 2 contingency tables. A two-tailed t-test was used to compare the values across groups.

We found that log transformation of circulating adipocytokines gave a better fit to a Gaussian distribution. The geometric mean for those biochemical variables was defined as the arithmetic mean of the log-transformed data ±SD, raised to the power of 10.

With adjustment for age, partial correlation analysis was performed to assess the association between circulating adipocytokines levels and biochemical variables.

The general linear model (GLM) univariate procedure was used for regression analysis and analysis of variance for adipocytokine levels (as dependent variables) by the studied groups (as independent variable). The covariates were age, BMI or WHR for GLM models.

The generalized linear models were conducted to examine the correlation between adipocytokines levels and the TNM staging for colorectal cancer defined by AJCC [28].

All statistical analyses were performed using the PASW Statistics GradPack 18 (SPSS Inc., Chicago, IL).

3. Results

Table 1 shows the general characteristics, including blood pressure, anthropometric measurements and biochemical parameters, of patients with CRC (39 subjects) compared with the control group (30 subjects). There were no significant differences in age, gender, systolic and diastolic blood pressure, WHR and BMI between the patients and the controls. There was also no significant difference in total cholesterol and HDL cholesterol between the two groups. However, the CRC group had higher LDL cholesterol and fasting blood glucose than the control group (p < 0.05, Table 1). In contrast, the control group had higher serum triglyceride levels than the CRC group (p < 0.05, Table 1).

Of the 69 participants, 2 (5.7%) and 3 (7.9%) subjects were smokers in the patient and control groups, respectively (p > 0.05). None of the participants had a history of alcohol consumption. There was no significant difference in prevalence of the metabolic syndrome between the patients and the controls (p > 0.05).

The results of the serum levels of the studied adipocytokines in both groups are shown as geometric means (± standard deviation) in Fig. 1. Compared with the controls, patients with CRC had significantly higher circulating visfatin, omentin-1 and vaspin levels (p < 0.0001, p < 0.0001 and p = 0.015, respectively).

No gender differences were found for the circulating visfatin, omentin-1 and vaspin (p > 0.05).

Age-adjusted correlations for serum visfatin, omentin-1 and vaspin in relation to anthropometric and biochemical measures were evaluated. Age-adjusted serum visfatin concentration levels were marginally correlated with WHR in the CRC group (r = 0.33, p = 0.045) and were significantly correlated with serum triglyceride (r = 0.42, p = 0.030) in the control group. However, there were no significant correlations between visfatin concentrations and BMI, fasting blood glucose and other lipid profile in both groups (p > 0.05).

Age-adjusted serum omentin-1 concentration levels were significantly correlated with LDL cholesterol (r = −0.39, p = 0.014) and total cholesterol levels (r = −0.404, p = 0.012) in patients with CRC. However, there were no significant correlations between omentin-1 concentrations and BMI, WHR, and fasting blood glucose in the CRC and control groups (p > 0.05).

Age-adjusted serum vaspin concentration levels were significantly correlated with fasting blood glucose (r = −0.36, p = 0.024) in the CRC group. However, there were no significant correlations between vaspin concentrations and other biochemical and anthropometric parameters in the patients with CRC and the controls (p > 0.05).

Table 2 shows the unadjusted and adjusted geometric mean ±SD for circulating adipocytokines (visfatin, omentin-1 and vaspin) levels stratified by the studied groups. After adjustment for covariates (age and BMI), patients with CRC had significantly higher serum visfatin (p < 0.0001), omentin-1 (p < 0.0001) and vaspin (p = 0.040) levels than the control group (Table 2). Furthermore, the results did not change when age and waist-to-hip ratio were considered covariates in the general linear models (Table 2).

The significant differences in serum adipocytokines concentrations between the patients with CRC and the controls did not also change when the metabolic syndrome were considered as predictor in the generalized linear models.

Among 30 patients with CRC; 2 cases were stage I, 9 cases were stage IIA, 4 cases were stage IIB, 3 cases were stage IIIA, 5 cases

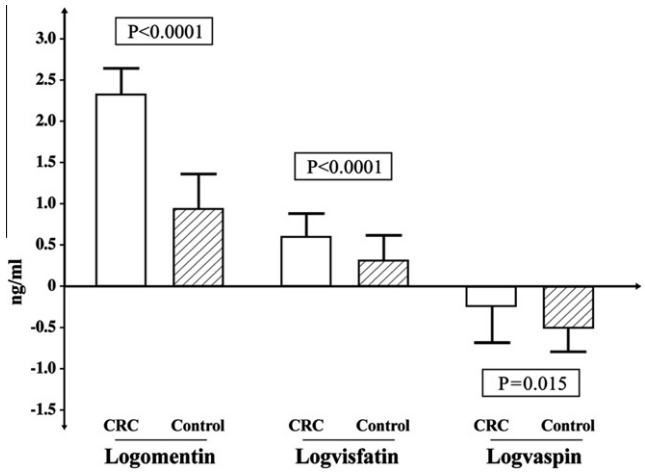

Fig. 1. Log transformed serum visfatin, vaspin and omentin-1 concentrations in patients with colorectal cancer (CRC, n = 39) and healthy controls (n = 30). Data are means ± standard deviation.

Table 2
Unadjusted and adjusted (age, BMI and WHR) circulating levels of adipocytokines in patients with colorectal cancer (CRC), compared with healthy controls.

	Visfatin (ng/ml)			Vaspin (ng/ml)			Omentin-1 (ng/ml)		
	CRC	Control	*p* Value	CRC	Control	*p* Value	CRC	Control	*p* Value
Unadjusted	4.03 (1.72)	2.01 (2.16)	<0.0001	0.54 (2.57)	0.31 (2.16)	0.015	203.23 (2.10)	9.12 (2.58)	<0.0001
Age-, and BMI-adjusted	4.10 (1.72)	1.99 (2.18)	<0.0001	0.55 (2.60)	0.30 (2.18)	0.025	202.76 (2.12)	8.95 (2.61)	<0.0001
Age-, and WHR-adjusted	4.09 (1.73)	1.99 (2.18)	<0.0001	1.79 (2.63)	0.30 (2.81)	0.027	201.37 (2.14)	8.95 (2.61)	<0.0001

Data are geometric means (standard deviation).
BMI = body mass index, WHR = waist-to-hip ratio

were stage IIIB, 4 cases were stage IIIC, 3 cases were stage IVA. There were no significant correlations between circulating adipocytokine levels and the TNM staging for colorectal cancer ($p > 0.05$).

4. Discussion

The patients with CRC had significantly increased levels of visfatin, omentin-1 and vaspin compared with the control subjects. The observed higher levels of these novel adipocytokines in the CRC group were independent of measures of adiposity.

PBEF1 (PBEF1/Nampt/Visfatin) has been reported to be overexpressed in primary CRC [22,29]. Later, in agreement with our results, Nakajima et al. found that visfatin levels in patients with CRC were significantly higher than those of the controls [9].

PBEF1/Nampt/Visfatin is a multifactional protein that converts nicotinamide to nicotinamide mononuclide, which is a key nicotinamide adenine dinucleotide (NAD) intermediate. PBEF1/Nampt/Visfatin also functions as a cytokine and shows adipocytokine activities [19]. These various functional aspects of PBEF1/Nampt/Visfatin illustrate its potential role in linking NAD biology with metabolism, inflammation and cancer [19,30].

The mechanisms by which PBEF1/Nampt/Visfatin-mediated NAD biosynthesis influences carcinogenesis have not been discovered. PBEF1/Nampt/Visfatin-mediated NAD biosynthesis is involved in inflammation, cellular differentiation, and tumor progression through downstream regulators such as sirtuins and poly (ADP-ribose) polymerase (PARP). The sirtuins are known to regulate both cell survival and tumor necrosis factor (TNF) secretion [19,30].

More investigations on the PBEF1/Nampt/Visfatin-mediated regulation of carcinogenesis through sirtuins are warranted in order to clarify the underlying mechanisms of the association of visfatin with CRC, which was observed in our study.

Nakajima et al. reported gradually increased visfatin levels with tumor progression [9]. However, we did not find significant correlations between circulating adipocytokine levels and the TNM staging for colorectal cancer defined by AJCC in generalized linear models.

We did not find a significant correlation between visfatin levels and BMI in either the CRC patients or the controls. The concentration of circulating visfatin in relation to obesity is controversial [31–33]. In a recent study [34], PBEF1/Nampt/Visfatin mRNA levels were not correlated with measures of obesity, and the researchers suggested that visfatin is not predominantly secreted from visceral fat.

Omentin-1 is a newly identified depot-specific adipocytokine in human adipose tissue that enhances insulin action [24]; it is inversely related to obesity [35] and is down regulated by insulin and glucose [36].

Omentin-1 enhances Akt phosphorylation/activation in the absence and presence of insulin [25]. Novel data for the role of omentin-1 in angiogenesis through the Akt signaling pathway has been provided [37].

Akt kinases are not only vital for the regulation of essential cellular functions, including proliferation, apoptosis, metabolism and transcription, but also for the regulation of vascular permeability, angiogenic responses and subsequent vascular maturation [38]. As neoangiogenesis and vascular leakage are important for angiogenesis-dependent pathologies, Akt signaling is believed to play a crucial role in carcinogenicity [39]. Itoh et al. showed that Akt activation plays an important role during the progression of CRC by enhancement of cell proliferation activity and the blocking of apoptosis [40]. In addition, endothelial nitric oxide synthase (eNOS), a downstream target of Akt, has been shown to be important in tumorigenesis, including colorectal carcinogenesis [41,42]. The eNOS polymorphisms in relation to colorectal cancer risk were also investigated [42].

The Akt cascade is activated by stimuli that induce the production of phosphatidylinositol 3,4,5 triphosphates by phosphoinositide 3-kinase (PI3K) [43]. Lim et al. suggested that the activation of PI3K/Akt-eNos signaling transduction is required during initiation and maintenance of oncogenic Ras-driven tumour growth [41]. Ras-gene mutations were found in 58% of colonic adenomas larger than 1 cm and in 47% of CRC [44].

Thus, there is sufficient evidence that the PI3K/Akt-eNos Ras pathway may be involved in colorectal-tumor development. Since omentin-1 enhances Akt phosphorylation/activation [24], it can be hypothesized that omentin-1, by promoting activation of the Akt signaling pathway and in turn modulating eNOS, may contribute in the pathogenesis of CRC.

Vaspin (visceral adipose tissue-derived serine protease inhibitor), a recently identified adipocytokine, has been suggested to have an insulin-sensitizing effect [25]. The circulating levels and tissue expression of vaspin increased at the peak of obesity and insulin resistance in Otsuka Long-Evans Tokushima fatty (OLETF) rats, an animal model of abdominal obesity and type 2 diabetes mellitus [45]. In the current study, for the first time, we found that patients with CRC had higher circulating levels of vaspin, in comparison with the controls. Thus, similar to omentin-1, vaspin may also be involved in carcinogenicity. However, the exact mechanism underlying vaspin in relation to cancer growth remains to be elucidated. Recently, Jung et al. [46] reported that vaspin protects vascular endothelial cells against free fatty acid-induced apoptosis through upregulation of the PI3K/Akt signaling pathway. Therefore, it can be hypothesized that vaspin may affect the PI3K/Akt pathway, produce cell proliferation activity, and prevent apoptosis.

We acknowledge several limitations in our study. A major limitation is the study's cross-sectional nature. Thus, limited inferences can be made regarding causality. Since we assessed the investigated adipocytokines with single measurements, the changes in these adipocytokines over time could not be reflected in the current study. The sample size was small, which may have affected our statistical power. In the current study, indices of insulin resistance were not measured. Another limitation of our study includes the lack of the TNM staging information for approximately one fourth of patients with CRC. Some novel adipocytokines were reported to be good biomarkers of the stage progression of CRC [9]. The measurement of additional adipocytokines and inflammatory markers and cytokines merits consideration in order to elucidate the "adipocytokines and cancer complex system".

In conclusion, circulating visfatin, omentin-1 and vaspin levels differed significantly between the patients with CRC and the controls. The association of higher levels of these novel adipocytokines with CRC remained after further adjustment for BMI or WHR. Our findings suggest that these adipocytokines may have a potential role in the development of CRC through mechanisms other than the indirect mechanisms that are active in the association of obesity and CRC. Integrative pathophysiological approaches are warranted to clarify this intermingled "adipocytokines and cancer complex system". The elucidation of this complex system will undoubtedly produce promising and novel pharmacological insights for treatment of CRC in the future.

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